10/046,616

C of C

HESLIN ROTHENBERG FARLEY & MESITI P.C.

INTELLECTUAL PROPERTY LAW

PATENTS • TRADEMARKS • COPYRIGHTS

Attorneys at Law
5 Columbia Circle
Albany, New York 12203
Telephone: (518) 452-5600
Facsimile: (518) 452-5579
www.hrfmlaw.com

Robert E. Heslin
Jeff Rothenberg
Kevin P. Radigan
Susan E. Farley
Nicholas Mesiti
Philip E. Hansen*
Blanche E. Schiller
Wayne F. Reinke
David P. Miranda

*Patent Agent

Kathy Smith Dias
David A. Pascarella
Victor A. Cardona
Lee Palmateer
John Pietrangelo*
Brett M. Hutton
Stephen M. Hladik
Edward Timmer
Alana M. Fuierer
John W. Boger

Of Counsel
Martha L. Boden
Jill M. Breedlove

Joseph L. Spiegel
Poughkeepsie, NY

August 23, 2005

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Re: Correction of Mistake in Printed Patent
Under §1480 of the Manual of Patent
Examining Procedures
U.S. Patent No.: 6,919,347
Date of Patent: July 19, 2005
Inventor(s): Ohlmeyer et al.
Our File No.: 1073.035A

Dear Sir:

Upon proofreading the sealed patent, we noticed errors made by the Patent Office.

Transmitted herewith is a proposed Certificate of Correction effecting a corrective amendment.

The patentee respectfully solicits the granting of the requested Certificate of Correction.

Respectfully submitted,

Edward Timmer

Edward Timmer, Esq.
Registration No. 46,248
Attorney for Applicants

ET/cma
Enclosure

N:\USERS\1073 Pharmacopeia\1073035A\TO PTO\1073035A-COCLTR-PTO.DOC
August 23, 2005

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO.	6,919,347
DATED	July 19, 2005
INVENTOR(S)	Ohlmeyer et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

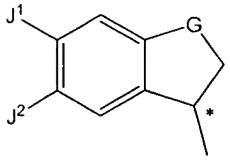
Claim 13

Col. 282, line 26, delete "A is R^4R^5N–(O)–;" and insert --A is R^4R^5N–C(O)–;--

Claim 14

Col. 283, lines 26 thru 32 structure

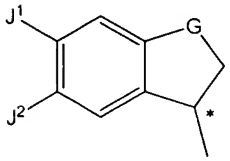
Delete current structure and replace with



Claim 15

Col. 284, lines 5 thru 10 structure

Delete current structure and replace with



2005

Claim 16

Col. 284, line 28, delete "A^1 is $R^4R^5N–C(O)–$;" and insert --A^1 is $R^4R^5N–C(O)–$,--

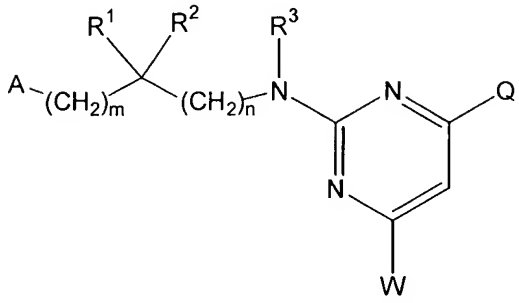
Claim 19

Col. 286, line 21, delete "C—C_3" in the second instance and insert –C_1—C_3

Claim 26

Col. 288, lines 3 thru 10 structure

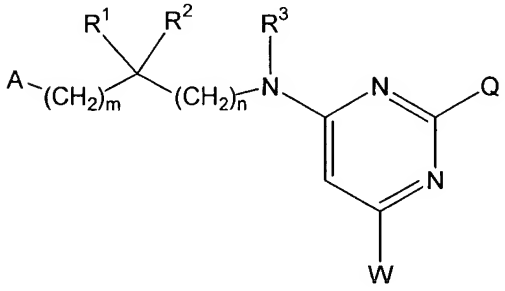
Delete current structure which has a "." after the letter "Q", and replace with



Claim 31

Col. 288, lines 57 thru 64

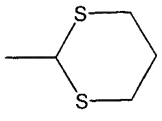
Delete current structure which has a "." after the letter "Q", and replace with



Claim 62

Col. 295, lines 41 thru 48

Delete current structure and replace with



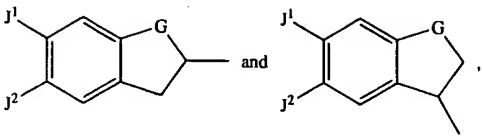
;

MAILING ADDRESS OF SENDER:
Edward Timmer, Esq.
Heslin Rothenberg Farley & Mesiti P.C.
5 Columbia Circle
Albany, New York 12203
Telephone: (518) 452-5600
Facsimile: (518) 452-5579

PATENT NO.:

No. of add'l copies
@ .50 per page

2005



wherein J^1 and J^2 are independently chosen from H, F, Cl, CN, NO_2 and CH_3, and G is chosen from —CH_2—, —CH_2CH_2—, —$CH_2CH_2CH_2$—, —OCH_2—, —CH_2O—, —CH_2CH_2O—, —OCH_2CH_2—, —O—, —N(lower alkyl)-, —N(lower alkyl)CH_2—, —CH_2N(lower alkyl)-, —S—, —SO—, —SO_2—, —CH_2S—, —SCH_2—, —CH_2SO—, —$SOCH_2$—, —CH_2SO_2—, and —SO_2CH_2—;

R^5 is H or C_1–C_3-alkyl, with the proviso that both R^3 and R^5 cannot be alkyl;

R^6 is aryl;

R^7 is aryl or C_1–C_3-alkylaryl;

R^8 is chosen from alkyl, aryl, heteroaryl, substituted alkyl, C_1–C_4-alkylaryl, C_1–C_4-alkylheterocyclyl and C_1–C_4-alkylheteroaryl;

R^9 is chosen from H, alkyl, alkenyl, substituted alkyl, cycloalkyl, aryl, alkoxy, heteroaryl, fluoroalkyl, C_1–C_4-alkylcycloalkyl, (C_1–C_4-alkoxy)alkyl, (C_1–C_4-alkoxycarbonyl)alkyl, (C_1–C_4-alkylthio)alkyl, heterocyclyl, C_1–C_4-alkylheterocyclyl, C_1–C_4-alkylaryl, and C_1–C_4-alkylheteroaryl;

R^{10} is H or C_1–C_3-alkyl; or

R^9 and R^{10} taken together may form a 5- to 7-membered ring structure optionally containing O, S, SO, SO_2 or NR^{12}, said ring optionally substituted with —OH, CN, —COOH or —$COOCH_3$;

R^{11} is aryl;

R^{12} is chosen from H, C_1–C_3-alkyl, alkoxycarbonyl, methoxyacetyl and aryl;

R^{13} is chosen from —OH, —OTHP, 1-imidazolyl, and 1-pyrrolyl;

m is zero or one; and

n is zero or one, with the proviso that when A is A^2, m and n cannot both be zero.

10. A 2-pyrimidinamine according to claim **9** wherein Q is chosen from imidazolyl, pyrrolyl, pyridinyl, fluorophenyl and 2-thienyl.

11. A 2-pyrimidinamine according to claim **10** wherein

A is R^4R^5N—C(O)—;

W is H, Cl, NHR^9 or OR^8;

R^1 is chosen from alkyl and C_1–C_3-alkylcycloalkyl;

R^2, R^3 and R^5 are H;

R^4 is C_1–C_4-alkylaryl or C_1–C_4-alkylheteroaryl;

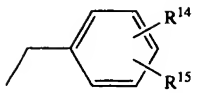
R^8 is C_1–C_4-alkylaryl;

R^9 is chosen from hydrogen, alkyl, fluoroalkyl, (C_1–C_4-alkoxy)alkyl, (C_1–C_4-alkylthio)alkyl, C_1–C_4-alkylcycloalkyl, C_1–C_4-alkylaryl, heterocyclyl, C_1–C_4-alkylheteroaryl, C_1–C_4-alkylheterocyclyl; and

m and n are zero.

12. A 2-pyrimidinamine according to claim **11** wherein W is NHR^9 and

R^9 is

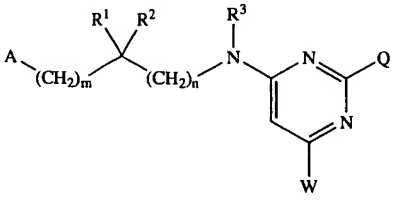


wherein

R^{14} is chosen from H, F, Cl, CN, NO_2, SO_2NH_2, CF_3, $COOCH_3$, OCH_3, SO_2CH_3, $N(CH_3)_2$ and COOH; and

R^{15} is chosen from H, OCH_3 and Cl.

13. A compound of formula



wherein:

A is R^4R^5N—C(O)—;

Q is is chosen from imidazolyl and pyrrolyl;

W is NHR^9;

R^1 is chosen from cyclohexylmethyl; 2-methylpropyl and 3-methyl-1-butyl;

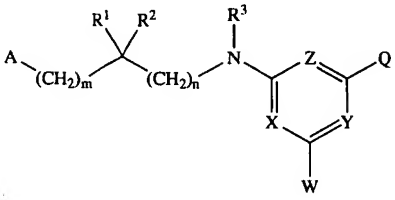
R^2, R^3 and R^5 are H;

R^4 and R^9 are benzyl or substituted benzyl;

m is zero; and

n is zero.

14. A compound of formula

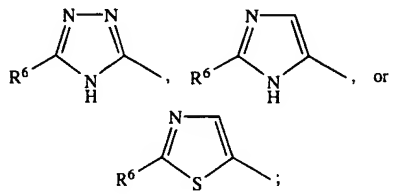


wherein:

two of X, Y and Z are N and the other of X, Y and Z is CH;

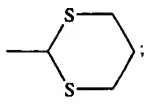
A is A^1 or A^2;

A^1 is R^4R^5N—C(O)—,



A^2 is chosen from $R^7C(O)NH$—, $R^7S(O)_2NH$—, R^4NH—, and R^4O—;

Q is chosen from heteroaryl, aryl, —CH_2R^{13}, —CH=N—OCH_3 and



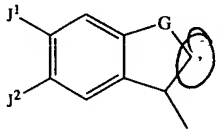
W is chosen from H, Cl, F, R^8, C_1–C_4-alkylaryl, —OR^8, —SR^8, —NR^9R^{10} and —$NHC(O)R^{11}$, with the proviso that when Q is imidazolyl, W is not H, Cl, F or R^8;

R^1 is chosen from alkyl, cycloalkyl, alkenyl, C_1–C_3-alkylcycloalkyl, heterocyclyl, C_1–C_3-alkylheterocyclyl, aryl, C_1–C_3-alkylaryl, heteroaryl, C_1–C_3-alkylheteroaryl, (C_1–C_3-alkyloxy)alkyl, (C_1–C_3-alkyloxy)cycloalkyl, (C_1–C_3-alkylthio)alkyl, (C_1–C_3-alkylthio)cycloalkyl and (C_1–C_3-alkylsulfonyl)alkyl;

R^2 is H or C_1–C_3-alkyl, or R^1 and R^2 taken together form a 5- to 7-membered ring structure optionally containing O, S or NR^{12};

R^3 is H or C_1–C_6-alkyl, or, when n is zero, R^2 and R^3 taken together may form a 6-membered ring, which may be fused to a six-membered saturated or aromatic carbocycle;

R^4 is



should be an * asterisk

having the R configuration at the carbon indicated with an asterisk, wherein J^1 and J^2 are independently chosen from H, F, Cl, CN, NO_2 and CH_3, and G is chosen from —CH_2—, —CH_2CH_2—, —$CH_2CH_2CH_2$—, —OCH_2—, —CH_2O—, —CH_2CH_2O—, —OCH_2CH_2—, —O—, —N(lower alkyl)-, —N(lower alkyl)CH_2—, —CH_2N(lower alkyl)-, —S—, —SO—, —SO_2—, —CH_2S—, —SCH_2—, —CH_2SO—, —$SOCH_2$—, —CH_2SO_2—, and —SO_2CH_2—;

R^5 is H or C_1–C_3-alkyl, with the proviso that both R^3 and R^5 cannot be alkyl;

R^6 is aryl;

R^7 is aryl or C_1–C_3-alkylaryl;

R^8 is chosen from alkyl, aryl, heteroaryl, substituted alkyl, C_1–C_4-alkylaryl, C_1–C_4-alkylheterocyclyl and C_1–C_4-alkylheteroaryl;

R^9 is chosen from H, alkyl, alkenyl, substituted alkyl, cycloalkyl, aryl, alkoxy, heteroaryl, fluoroalkyl, C_1–C_4-alkylcycloalkyl, (C_1–C_4-alkoxy)alkyl, (C_1–C_4-alkoxycarbonyl)alkyl, (C_1–C_4-alkylthio)alkyl, heterocyclyl, C_1–C_4-alkylheterocyclyl, C_1–C_4-alkylaryl, and C_1–C_4-alkylheteroaryl;

R^{10} is H or C_1–C_3-alkyl; or

R^9 and R^{10} taken together may form a 5- to 7-membered ring structure optionally containing O, S, SO, SO_2 or NR^{12}, said ring optionally substituted with —OH, —CN, —COOH or —$COOCH_3$;

R^{11} is aryl;

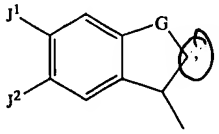
R^{12} is chosen from H, C_1–C_3-alkyl, alkoxycarbonyl, methoxyacetyl and aryl;

R^{13} is chosen from —OH, —OTHP, 1-imidazolyl, and 1-pyrrolyl;

m is zero or one; and

n is zero or one, with the proviso that when A is A^2, m and n cannot both be zero.

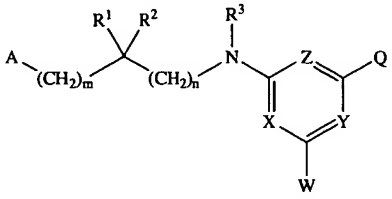
15. A pyrimidine according to claim **9** wherein R^4 is



should be an * asterisk

having the R configuration at the carbon indicated with an asterisk.

16. A compound of formula

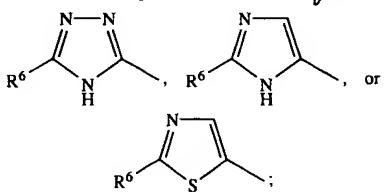


wherein:

two of X, Y and Z are N and the other of X, Y and Z is CH;

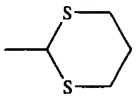
A is A^1 or A^2;

A^1 is R^4R^5N—C(O)—; should be a comma



A^2 is chosen from $R^7C(O)NH$—, $R^7S(O)_2NH$—, R^4NH—, and R^4O—;

Q is chosen from aryl, —CH_2R^{13}, —CH=N—OCH_3 and



heteroaryl other than 1-imidazolyl and 1-triazolyl;

W is chosen from H, Cl, F, R^8, C_1–C_4-alkylaryl, —OR^8, —SR^8, —NR^9R^{10} and —$NHC(O)R^{11}$, with the proviso that when Q is imidazolyl, W is not H, Cl, F or R^8;

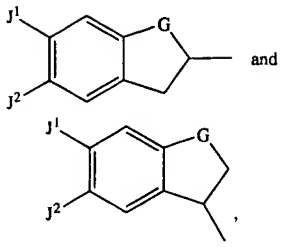
R^1 is chosen from alkyl, cycloalkyl, alkenyl, C_1–C_3-alkylcycloalkyl, heterocyclyl, C_1–C_3-alkylheterocyclyl, aryl, C_1–C_3-alkylaryl, heteroaryl, C_1–C_3-alkylheteroaryl, (C_1–C_3-alkyloxy)alkyl, (C_1–C_3-alkyloxy)cycloalkyl, (C_1–C_3-alkylthio)alkyl, (C_1–C_3-alkylthio)cycloalkyl and (C_1–C_3-alkylsulfonyl)alkyl;

R^2 is H or C_1–C_3-alkyl, or R^1 and R^2 taken together form a 5- to 7-membered ring structure optionally containing O, S or NR^{12};

R^3 is H or C_1–C_6-alkyl, or, when n is zero, R^2 and R^3 taken together may form a 6-membered ring, which may be fused to a six-membered saturated or aromatic carbocycle;

R^4 is chosen from H, aryl, heteroaryl, C_1–C_4-alkyl substituted with from one to three aryl or heteroaryl

residues,



wherein J^1 and J^2 are independently chosen from H, F, Cl, CN, NO_2 and CH_3, and G is chosen from —CH_2—, —CH_2CH_2—, —$CH_2CH_2CH_2$—, —OCH_2—, CH_2O—, —CH_2CH_2O—, —OCH_2CH_2—, —O—, —N(lower alkyl)-, —N(lower alkyl)CH_2—, —CH_2N(lower alkyl)-, —S—, —SO—, —SO_2—, —CH_2S—, —SCH_2—, —CH_2SO—, —$SOCH_2$—, —CH_2SO_2—, and —SO_2CH_2—;

R^5 is H or C_1–C_3-alkyl, with the proviso that both R^3 and R^5 cannot be alkyl;

R^6 is aryl;

R^7 is aryl or C_1–C_3-alkylaryl;

R^8 is chosen from alkyl, aryl, heteroaryl, substituted alkyl, C_1–C_4-alkylaryl, C_1–C_4-alkylheterocyclyl and C_1–C_4-alkylheteroaryl;

R^9 is chosen from H, alkyl, alkenyl, substituted alkyl, cycloalkyl, aryl, alkoxy, heteroaryl, fluoroalkyl, C_1–C_4-alkylcycloalkyl, (C_1–C_4-alkoxy)alkyl, (C_1–C_4-alkoxycarbonyl)alkyl, (C_1–C_4-alkylthio)alkyl, heterocyclyl, C_1–C_4-alkylheterocyclyl, C_1–C_4-alkylaryl, and C_1–C_4-alkylheteroaryl;

R^{10} is H or C_1–C_3-alkyl, or

R^9 and R^{10} taken together may form a 5- to 7-membered ring structure optionally containing O, S, SO, SO_2 or NR^{12}, said ring optionally substituted with —OH, —CN, —COOH or —$COOCH_3$;

R^{11} is aryl;

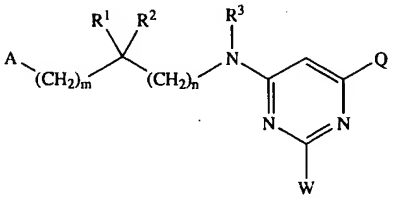
R^{12} is chosen from H, C_1–C_3-alkyl, alkoxycarbonyl, methoxyacetyl and aryl;

R^{13} is chosen from —OH, —OTHP, 1-imidazolyl, and 1-pyrrolyl;

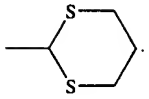
m is zero or one; and

n is zero or one, with the proviso that when A is A^2, m and n cannot both be zero.

17. A 4-pyrimidinamine according to claim **16**, wherein Z is CH, having the formula



18. A 4-pyrimidinamine according to claim **17** wherein Q is chosen from methylimidazolyl, pyrrolyl, methylpyrrolyl, pyrazolyl, methylpyrazolyl, furanyl, methylfuranyl, thienyl, oxazolyl, thiazolyl, pyridinyl, quinolinyl, 1-methylpyrimidin-2-onyl, phenyl, fluorophenyl, hydroxymethyl, 2-imidazolyl, tetrahydropyranyloxymethyl, imidazolylmethyl, pyrrolylmethyl, —CH=N—OCH_3 and

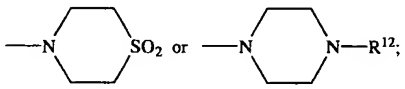


19. A 4-pyrimidinamine according to claim **18** wherein:

Q is chosen from pyrrol-1-yl, imidazol-1-yl, furan-3-yl, 2-methylimidazol-1-yl and 4-methylimidazol-1-yl;

A is R^4R^5N—C(O)—;

W is Cl, NRH^9, $N(CH_3)R^9$, OR^8, SR^8, R^8, morpholin-4-yl,



R^1 is chosen from alkyl, cycloalkyl, C_1–C_3-alkylaryl, C_1–C_3-alkylcycloalkyl, C—C_3-alkylheterocyclyl, C_1–C_3-alkylheteroaryl;

R^2, R^3 and R^5 are H;

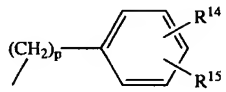
R^8 is C_1–C_4-alkylaryl;

R^9 is chosen from hydrogen, alkyl, substituted alkyl, (C_1–C_4)-alkoxy, C_1–C_4-alkylcycloalkyl, C_1–C_4-alkylaryl, heterocyclyl, C_1–C_4-alkylheteroaryl, C_1–C_4-alkylheterocyclyl; and

m and n are zero.

20. A 4-pyrimidinamine according to claim **19** wherein W is NHR^9 and

R^9 is chosen from hydrogen; methyl; ethyl; 2,2,2-trifluoroethyl; allyl; cyclopropyl; 2-cyanoethyl; propargyl; methoxy; methoxyethyl; cyclopropyl; cyclopropylmethyl; (methylthio)ethyl; 3-methoxypropyl; 3-pyridyl; 2-(3-pyridyl)ethyl; 2-(2-pyridyl)ethyl; 3-pyridylmethyl; 4-pyridylmethyl; 4-pyridylmethyl-N-oxide; 2-pyridazinylmethyl; sulfolan-3-yl; 3-tetrahydrofuranyl; 2-tetrahydrofuranylmethyl; 3-(1-imidazolyl)propyl; 1-t-butoxycarbonyl-4-piperidinyl; 1-t-butoxycarbonyl-4-piperidinylmethyl; 2-(hydroxyimino)propyl; 2-(methoxyimino)propyl; 2-oxo-1-propyl; and



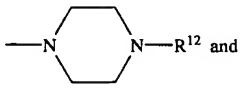
wherein

R^{14} is chosen from H, Cl, F, CN, NO_2, SO_2NH_2, CF_3, $COOCH_3$, OCH_3, OH, SO_2CH_3, $N(CH_3)_2$ and COOH;

R^{15} is chosen from H, OCH_3 and Cl; and

p is 1 or 2.

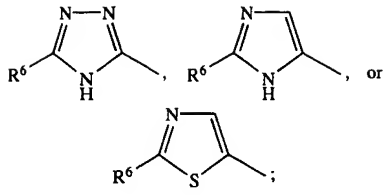
21. A 4-pyrimidinamine according to claim **19** wherein W is



R^{12} is t-butoxycarbonyl, methoxyacetyl or phenyl.

22. A 4-pyrimidinamine according to claim **16** wherein Z is CH;

A is



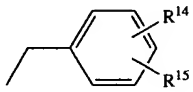
R^1 is chosen from n-butyl; cyclohexylmethyl; cyclopentylmethyl; 2-methylpropyl; 3-methyl-1-butyl; cyclohexyl; 2,2-dimethylpropyl; benzyl; 2-thienylmethyl; 1-t-butoxycarbonyl-4-piperidinyl; 4-chlorobenzyl; 2-pyranylmethyl; 4-pyranylmethyl; 4-pyranyl and 1,1-dimethylethyl;

R^2 and R^3 are H;

Q is pyrrolyl;

W is NHR^9; and

R^9 is alkyl, cycloalkyl or



wherein

R^{14} is chosen from H, Cl, F, CN, NO_2, SO_2NH_2, CF_3, $COOCH_3$, OCH_3, SO_2CH_3, $N(CH_3)_2$ and COOH; and

R^{15} is chosen from H, OCH_3 and Cl.

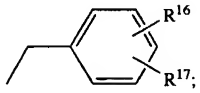
23. A pyrimidine according to claim **16** wherein:

A is R^4R^5N—C(O)—;

R^1 is chosen from isopropyl; n-butyl; cyclohexylmethyl; cyclopentylmethyl; naphthylmethyl; cyclohexylethyl; 2-methylpropyl; 3-methyl-1-butyl; cyclohexyl; 2,2-dimethylpropyl; benzyl; 2-thienylmethyl; 1-t-butoxycarbonyl-4-piperidinyl; 4-methoxybenzyl; 4-chlorobenzyl; 3,4-dichlorobenzyl; 2-pyranylmethyl; 4-pyranylmethyl; 4-pyranyl and 1,1-dimethylethyl;

R^2, R^3 and R^5 are H;

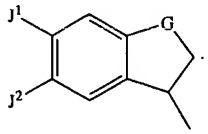
R^4 is pyridinyl, pyridinylmethyl, indanylmethyl, furanylmethyl, tetrahydronaphthalenyl, substituted phenyl, or



R^{16} is chosen from H, Cl, F, CN, NO_2, SO_2NH_2, CF_3, CH_3, $COOCH_3$, OCH_3, SO_2CH_3, $N(CH_3)_2$ and COOH; and

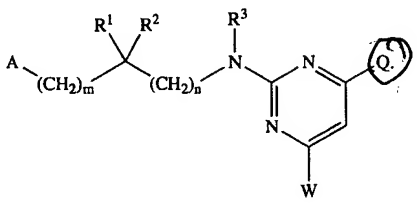
R^{17} is chosen from H, OCH_3, F and Cl.

24. A pyrimidine according to claim **16** wherein R^4 is



25. A pyrimidine according to claim **24**, wherein one of J^1 and J^2 is H and the other is H, Cl or CN and G is chosen from —CH_2—, —CH_2CH_2—, —OCH_2—, —O— and —CH_2N(lower alkyl)-.

26. A 2-pyrimidinamine according to claim **16**, wherein Y is CH, having the formula



27. A 2-pyrimidinamine according to claim **26** wherein Q is chosen from pyrrolyl, pyridinyl, fluorophenyl and 2-thienyl.

28. A 2-pyrimidinamine according to claim **27** wherein

A is R^4R^5N—C(O)—;

W is H, Cl, NHR^9 or OR^8;

R^1 is chosen from alkyl and C_1–C_3-alkylcycloalkyl;

R^2, R^3 and R^5 are H;

R^4 is C_1–C_4-alkylaryl or C_1–C_4-alkylheteroaryl;

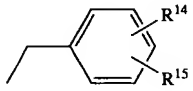
R^8 is C_1–C_4-alkylaryl;

R^9 is chosen from hydrogen, alkyl, fluoroalkyl, (C_1–C_4-alkoxy)alkyl, (C_1–C_4-alkylthio)alkyl, C_1–C_4-alkylcycloalkyl, C_1–C_4-alkylaryl, heterocyclyl, C_1–C_4-alkylheteroaryl, C_1–C_4-alkylheterocyclyl; and

m and n are zero.

29. A 2-pyrimidinamine according to claim **28** wherein W is NHR^9 and

R^9 is

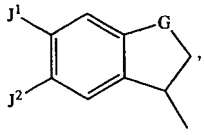


wherein

R^{14} is chosen from H, F, Cl, CN, NO_2, SO_2NH_2, CF_3, $COOCH_3$, OCH_3, SO_2CH_3, $N(CH_3)_2$ and COOH; and

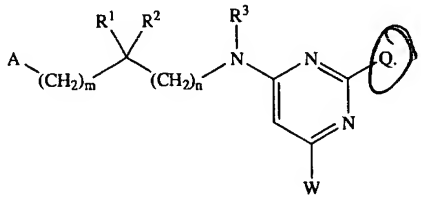
R^{15} is chosen from H, OCH_3 and Cl.

30. A 2-pyrimidineamine according to claim **26** wherein R^4 is



one of J^1 and J^2 is H and the other is H, Cl or CN and G is chosen from —CH_2—, —CH_2CH_2—, —OCH_2—, —O— and —CH_2N(lower alkyl)-.

31. A 4-pyrimidinamine according to claim **16**, wherein X is CH, having the formula

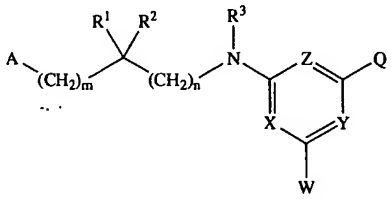


32. A 4-pyrimidinamine according to claim **31** wherein Q is pyrrolyl and m and n are zero.

60. The method of treating pain or hyperalgesia according to claim 59 wherein said cyclooxygenase inhibitor is a selective cyclooxygenase-2 inhibitor.

61. The method of treating pain or hyperalgesia according to claim 59 wherein said cyclooxygenase inhibitor is a selective cyclooxygenase-1 inhibitor.

62. A method of treating post-capillary resistance or diabetic symptoms associated with insulitis comprising administering to a subject in need of such treatment a therapeutically effective amount of a compound of formula I



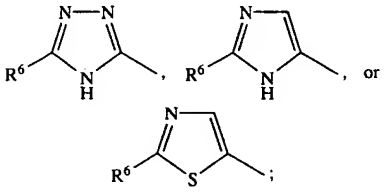
I

wherein:

two of X, Y and Z are N and the other of X, Y and Z is CH;

A is A^1 or A^2;

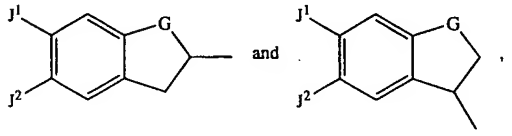
A^1 is R^4R^5N—(O)—,



;

A^2 is chosen from $R^7C(O)NH$—, $R^7S(O)_2NH$—, R^4NH—, and R^4O—;

Q is chosen from heteroaryl, aryl, $—CH_2R^{13}$, —CH=N—OCH_3 and



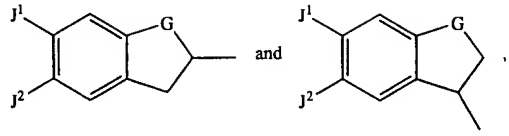
W is chosen from H, Cl, F, R^8, C_1–C_4-alkylaryl, $—OR^8$, $—SR^8$, $—NR^9R^{10}$ and $—NHC(O)R^{11}$, with the proviso that when Q is imidazolyl, W is not H, Cl, F or R^8;

R^1 is chosen from alkyl, cycloalkyl, alkenyl, C_1–C_3-alkylcycloalkyl, heterocyclyl, C_1–C_3-alkylheterocyclyl, aryl, C_1–C_3-alkylaryl, heteroaryl, C_1–C_3-alkylheteroaryl, (C_1–C_3-alkyloxy)alkyl, (C_1–C_3-alkyloxy)cycloalkyl, (C_1–C_3-alkylthio)alkyl, (C_1–C_3-alkylthio)cycloalkyl and (C_1–C_3-alkylsulfonyl)alkyl;

R^2 is H or C_1–C_3-alkyl, or R^1 and R^2 taken together form a 5- to 7-membered ring structure optionally containing O, S or NR^{12};

R^3 is H or C_1–C_6-alkyl, or, when n is zero, R^2 and R^3 taken together may form a 6-membered ring, which may be fused to a six-membered saturated or aromatic carbocycle;

R^4 is chosen from H, aryl, heteroaryl, C_1–C_4-alkyl substituted with from one to three aryl or heteroaryl residues,



wherein J^1 and J^2 are independently chosen from H, F, Cl, CN, NO_2 and CH_3 and G is chosen from $—CH_2—$, $—CH_2CH_2—$, $—CH_2CH_2CH_2—$, $—OCH_2—$, $—CH_2O—$, $—CH_2CH_2O—$, $—OCH_2CH_2—$, —O—, —N(lower alkyl)-, $—N(\text{lower alkyl})CH_2—$, $—CH_2N(\text{lower alkyl})-$, —S—, —SO—, $—SO_2—$, $—CH_2S—$, $—SCH_2—$, $—CH_2SO—$, $—SOCH_2—$, $—CH_2SO_2—$, and $—SO_2CH_2—$;

R^5 is H or C_1–C_3-alkyl, with the proviso that both R^3 and R^5 cannot be alkyl;

R^6 is aryl;

R^7 is aryl or C_1–C_3-alkylaryl;

R^8 is chosen from alkyl, aryl, heteroaryl, substituted alkyl, C_1–C_4-alkylaryl, C_1–C_4-alkylheterocyclyl and C_1–C_4-alkylheteroaryl;

R^9 is chosen from H, alkyl, alkenyl, substituted alkyl, cycloalkyl, aryl, alkoxy, heteroaryl, fluoroalkyl, C_1–C_4-alkylcycloalkyl, (C_1–C_4-alkoxy)alkyl, (C_1–C_4-alkoxycarbonyl)alkyl, (C_1–C_4-alkylthio)alkyl, heterocyclyl, C_1–C_4-alkylheterocyclyl, C_1–C_4-alkylaryl, and C_1–C_4-alkylheteroaryl;

R^{10} is H or C_1–C_3-alkyl; or

R^9 and R^{10} taken together may form a 5- to 7-membered ring structure optionally containing O, S, SO, SO_2 or NR^{12}, said ring optionally substituted with —OH, —CN, —COOH or $—COOCH_3$;

R^{11} is aryl;

R^{12} is chosen from H, C_1–C_3-alkyl, alkoxycarbonyl, methoxyacetyl and aryl;

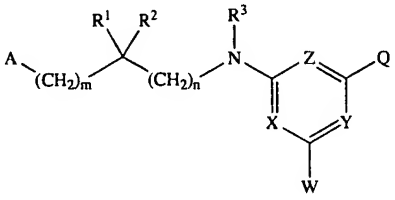
R^{13} is chosen from —OH, —OTHP, 1-imidazolyl, and 1-pyrrolyl;

m is zero or one; and

n is zero or one, with the proviso that when A is A^2, m and n cannot both be zero.

63. The method according to claim 62 wherein said diabetic symptoms associated with insulitis comprise hyperglycemia, diuresis, proteinuria and increased nitrile and kallikrein urinary excretion.

64. A method of treating edema comprising administering to a subject in need of such treatment a therapeutically effective amount of a compound of formula I



I

wherein:

two of X, Y and Z are N and the other of X, Y and Z is CH;

A is A^1 or A^2;